REMARKS

Applicants thank Examiner Afremova for her time and helpful discussion during the telephonic interview conducted with Applicant Dr. Susan Bonner-Weir and Applicant's attorney. During the interview, the prior art rejections were discussed. The substance of the interview is discussed herein below.

Claims 16, 31 and 44 have been canceled. Claims 14, 17, 29, 32, 41 and 45 have been amended. New claims 65-73 have been added. The amended and new claims are supported throughout the application as filed, e.g., page 14, lines 5-6; page 17, lines 5-11; page 32, lines 6-10, and by original claim 17. No new matter has been added.

Upon entry of this amendment, claims 1-73 will be pending and claims 14-26 and 29-73 will be under examination.

The Invention

The present claims are directed to methods of obtaining pancreatic islet cells from dedifferentiated pancreatic cells. The methods includes adding a component of the extracellular matrix (ECM) to a population of dedifferentiated pancreatic cells, and culturing the cells in the presence of the ECM component.

Dedifferentiated pancreatic cells are, as defined in the specification, adult or differentiated pancreatic cells that have been allowed to proliferate in culture, thereby having reverted to a less differentiated state, i.e., a pluripotent state. See, e.g., page 2, lines 1-5; page 32, lines 6-11. In order to better define the dedifferentiated cells, claims 14, 29 and 41 have been amended to recite that the dedifferentiated pancreatic cells are characterized by having undergone proliferation characterized by (a) lack insulin expression and (b) expression one or more of IPF-1, PDX-1, STF-1, IDX-1 and Pref-1 protein. The dedifferentiated (pluripotent) cells are then redifferentiated into mature islet cells by adding a component of ECM and growing them in the presence of the component.

Rejections Under 35 U.S.C. §102

Claims 14, 16, 17, 21-26, 29, 31, 32, 36-40 are rejected as anticipated by Kerr-Conte (Supplemental IDS of 9/27/2002, reference AH). During the interview, the Examiner indicated that the dedifferentiated cells recited in Applicants' claims were not distinguishable on the face of the claims from the cells used in Kerr-Conte. The Examiner suggested that the dedifferentiated cells be defined by specific characteristics in the claims. Applicants have amended to claims to recite additional characteristics of the dedifferentiated cells, as suggested by the Examiner. Namely, the claims have been amended to further characterize the dedifferentiated cells as having undergone proliferation characterized by (a) lack insulin expression and (b) expression one or more of IPF-1, PDX-1, STF-1, IDX-1 and Pref-1 protein.

Kerr-Conte does not anticipate the presently amended claims.

Kerr-Conte reports that they obtained expansion of ductal epithelial cells from a preparation of adult islet cells. Kerr-Conte teaches the following experimental conditions:

> Human islets from 9 donors (age 37 ± 5 years) were isolated as previously described with the semiautomated method and purified in Euro-Ficoll density gradients in the Cobe 2991 (purity >80%). Islets were resuspended (200 islets/mL gel) in rat tail type I collagen, Matrigel, purified type I collagen. (See Kerr-Conte Materials and Methods section, emphasis added.)

As can be seen in the above passage, Kerr-Conte teaches resuspending adult islets directly in an ECM component. In contrast, the present claims recite adding a component of ECM to a population of dedifferentiated pancreatic cells which have undergone proliferation characterized by (a) lack of insulin expression and (b) expression one or more of IPF-1, PDX-1, STF-1, IDX-1 and Pref-1 protein. Kerr-Conte does not mention or suggest that the islets are dedifferentiated as recited in the claims. Indeed, because adult islets by definition express insulin, the islets used by Kerr-Conte to which the collagen or Matrigel is added cannot have undergone proliferation characterized by lack of insulin expression, as recited in the claims. Accordingly, Kerr-Conte does not anticipate the present claims and Applicants respectfully request that the rejection be withdrawn.

Rejections Under 35 U.S.C. §103

Claims 14, 16, 17, 21-26, 29, 31, 32, 36-42, 44-45 and 47-51 are rejected as unpatentable over Kerr-Conte and Gmyr et al. (Supplemental IDS of 9/27/2002, reference AG). The Examiner provides the following arguments in support of the rejection.

> Kerr-Conte...teaches the use of mixed population of pancreatic cells for neogenesis of islet cells. However, it clearly indicates that the neogenesis of islets cells or neogenesis of endocrine cytodifferentiation raises from the expanded ductal epithelial cells which are positive for cytokeratin or which are positive for marker of dedifferentiated pancreatic cells. Thus, the references clearly teaches or suggests the use of pancreatic cell population free from islets cells for neogenesis of islet cells.
>
> The reference by Gmyr et al...teaches an *in vitro* method for dedifferentiation of exocrine cells or pancreatic cells free islets cells (*sic*) as evidenced by expression of cytokeratin markers. It also suggests the use of the expanded populations of dedifferentiated exocrine cells which are free islets cells for further endocrine differentiation into hormone producing islets cells.

This rejection is respectfully traversed insofar as it may be applied to the present claims. Kerr-Conte and Gmyr describe methods for obtaining duct cells, not islet cells as recited in the claims. Moreover, none of the methods described in Kerr-Conte or Gmyr disclose or suggest the limitation (present in all the claims) of adding a component of ECM to dedifferentiated cells, as recited in the claims.

As discussed above, Kerr-Conte reports that they obtained expansion of ductal epithelial cells from a preparation of 80% pure adult islet cells that were placed directly on collagen or Matrigel. Gmyr report obtaining ductal epithelium from: (A) adult pancreatic ducts that were directly cultured in serum as an explant; (B) adult islet cells that were directly resuspended on collagen; and (C) cultured exocrine cells. Neither of the cited references discloses or suggests using a population of dedifferentiated cells, i.e., adult pancreatic cells that have undergone proliferation characterized by lack of insulin expression and (ii) expression one or more of IPF-1, PDX-1, STF-1, IDX-1 and Pref-1 protein, much less adding a component of ECM to such cells, as required by the claims.

The Examiner states that Kerr-Conte discloses "the neogenesis of islets cells or neogenesis of endocrine cytodifferentiation raises from the expanded ductal epithelial cells which are positive for cytokeratin or which are positive for marker of dedifferentiated pancreatic cells." Applicants note that the ductal epithelial cells described in Kerr-Conte are in fact positive for carbohydrate antigen 19-9, which is a marker of differentiated ductal cells, not of dedifferentiated cells. Moreover, even if Kerr-Conte did suggest dedifferentiated cells as recited in the claims (which it clearly does not), Kerr-Conte certainly does not suggest the limitation of the claimed methods, namely to add a component of the ECM to a population of such dedifferentiated cells. To the contrary, Kerr-Conte teaches adding a component of ECM to adult, differentiated cells.

The Examiner also states that Gmyr "suggests the use of the expanded populations of dedifferentiated exocrine cells which are free islets cells for further endocrine differentiation into hormone producing islets cells." However, Gmyr does no such thing. Gmyr merely states "We are now *screening* various conditions to induce the endocrine differentiation of these ductal precursor cells" (emphasis added). This is clearly no more than an invitation to experiment. Gmyr does not even speculate about what such conditions might be.

The MPEP plainly states that the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the modification or combination. MPEP § 2143.01. It is insufficient that one reference theoretically be modified. Neither Kerr-Conte nor Gmyr, alone or in combination, teach the dedifferentiated cells as recited in the claims, nor provide any reason or motivation to make dedifferentiated cells as recited in the claims. Much less do they teach or suggest adding a component of the ECM to such dedifferentiated cells. Therefore, neither Kerr-Conte nor Gmyr, alone or in combination, suggest the presently claimed methods. Applicants respectfully request that the rejection be withdrawn.

Claims 18-20, 33-35, 46, 52-56 and 61-64 are rejected as unpatentable over Kerr-Conte and Gmyr et al. and further in view of US 4,829,000; US 5,681,587; and US 6,077,692. This rejection is respectfully traversed. As discussed in detail above, neither Kerr-Conte nor Gmyr, alone or in combination, teach or suggest dedifferentiated cells as recited in the claims, or any

reason to make them, nor to add a component of the ECM to such dedifferentiated cells. US 4,829,000; US 5,681,587; and US 6,077,692 describe various growth factors or components of ECM. However, none of the secondary patent references cited, alone or in combination, make up for the deficiencies of Kerr-Conte and Gmyr discussed above. Therefore, Applicants respectfully request that the rejection be withdrawn.

Claims 58-60 are rejected as unpatentable over Kerr-Conte and Gmyr et al. and further in view of WO 96/40872 and Carlsson et al. Claims 58-60 are now canceled, thereby obviating the rejection.

Claims 15, 30, 43 and 57 are rejected as unpatentable over Kerr-Conte and Gmyr et al. and further in view of US 4,439,521. This rejection is respectfully traversed. As discussed in detail above, neither Kerr-Conte nor Gmyr, alone or in combination, teach or suggest dedifferentiated cells as recited in the claims, or any reason to make them, nor to add a component of the ECM to such dedifferentiated cells. US 4,439,521 teaches the expansion of cultured cells to different degrees of confluency. US 4,439,521 does not make up for the deficiencies of Kerr-Conte and Gmyr as discussed above. Therefore, Applicants respectfully request that the rejection be withdrawn.